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Exploring the socioethical dilemmas in the use of a global health archive

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Abstract

A global health archive consisting of podoconiosis tissue slides and blocks (which was collected and imported into the UK before the introduction of the Human Tissue Act), was donated to Brighton & Sussex Medical School in 2014. There is little guidance on the socioethical and legal issues surrounding the retrospective use of archived or 'abandoned' tissue samples, which poses a number of questions relating to the ethical standing of the archive.

There is a great deal of interpretation in the guidelines that are currently in existence; however, modern ethical principles cannot be applied as it is not feasible to either reconsent or retrospectively seek approval. Our research team believed that it was unethical to leave the archive in storage, as this option favours neither researcher nor subjects. Permission was obtained from the Human Tissue Authority and a local ethics board for the tissues to be utilized in on-going research on podoconiosis aetiology.

There is a delicate balance between the benefits gained by society relating to the development and progress of scientific research and the risks to the donor regarding the reuse of their tissues. Clearer guidelines should be made available to ensure that researchers are able to reuse tissue archives in contemporary research.

Keywords

biobank, bioethics, ethics, global health, podoconiosis, tissue bank

Introduction

Guidance on the socioethical and legal issues around biobanks has evolved rapidly over the past two decades, driven chiefly by the expansion of DNA repositories. Biomedical researchers widely acknowledge the importance of access to human tissues, but the public perception of tissue storage and biobanking was profoundly impacted in the UK after several high-profile incidents of human tissue misuse such as at Alder Hey Hospital (Burton and Wells, 2002). Despite the expansion of such biorepositories, guidance available has typically focused prospectively on the collection of samples, access to personal information and methods of anonymization. Comparatively little guidance exists on the retrospective use of archived or abandoned samples originating from medical care or earlier research, specifically the ethical implications and research governance requirements of using archived or abandoned samples.

Over the past two decades, strict legislation has been implemented to guide scientists and medical professionals on the use of human tissues that have been excised as part of a treatment or diagnostic test. The 1995 Nuffield report on the legal and ethical issues surrounding human tissues recommends that patients receiving a treatment or diagnostic test should also be consented to the subsequent disposal or storage of tissue and to further acceptable uses (at some point in time), that are regulated by appropriate legal, ethical and professional standards (McLean, 1995). However, there is a considerable amount of biological material currently in

existence that predates this guidance and, as such, does not have the appropriate consent for continued usage in contemporary research.

A gifted archive

We present our experience at Brighton and Sussex Medical School (BSMS) of housing and using a gifted global health archive for contemporary research. It is not uncommon for biological material to be gifted to academic institutions; however, it falls to the role of the archivist to clarify the ethical standing of the tissue repository, which can often be challenging. The archive in question is a collection of materials relating to podoconiosis (non-filarial elephantiasis), a geochemical tropical lymphoedema. The disease is a reaction to mineral particles in the legs of people exposed to certain volcanic soils, particularly in Ethiopia and Cameroon. Dr Ernest Price, a British leprologist who worked in Africa between the 1950s and 1980s and was the first person to identify the association between podoconiosis and exposure to irritant soils, collected the materials throughout his career. The archive consists of tissue thin sections mounted onto microscope slides and tissue embedded in blocks of resin from patients, and written materials documenting his work across Africa, as well as some of the analysis that he carried out on the materials back in the UK. After Dr Price's death in 1990, the collection was stored in his son's attic for over 20 years before being gifted to BSMS, the hub of podoconiosis research over the past decade.

This is a unique collection; to the authors' knowledge, no other collection of samples from podoconiosis patients exists anywhere in the world. The benefits gained from the use of Price's archive will translate into greater understanding of the underlying aetiology and pathogenesis of podoconiosis, and thus directly into the intervention and treatment programmes that are currently established in areas of Ethiopia and Cameroon, from where the tissues originated.

As soon as the gift was made, the BSMS Research Governance and Ethics Committee was alerted to the presence of the archive and offered guidance on its storage, particularly in relation to the Human Tissue Act (HTA). The Human Tissue Authority was also made aware of the archive, but agreed that further licensing was unnecessary given the HTA licence already held by BSMS.

The BSMS archivist and podoconiosis researchers needed to consider a number of factors including the age of the archive and the lack of knowledge of the ethical frameworks that were in place in the countries of origin at that time, which meant that it was problematic to determine exactly what purposes the archive could be used for. Owing to the governance challenges of obtaining human tissue samples overseas and importing them back to the UK and the value of the samples, the research team was keen to use this unique archive to study the disease's underlying pathogenesis, which is still poorly understood.

We set out three key questions to determine the ethical standing of the archive. Are we correct to apply current ethical standards retrospectively? What guidance currently exists on the use of a historical archive in contemporary research? Is it unethical not to use the archive?

Are we correct to apply current ethical standards retrospectively?

Firstly, we considered the ethical principles and guidelines that were in place when the collection was first established. Clearly, these principles have evolved over the past four decades, but it was important to understand the ethical landscape of the time and whether this might have a bearing on the archive's potential use in contemporary research. Another consideration was whether these principles were upheld in practice when the archive was established and, if so, what safeguards were in place to ensure that they were maintained.

Several studies conducted in the USA during the 1970s guided the establishment of national and international regulatory ethical frameworks. The infamous Stanford prison experiment took place in 1971, and the National Research Act was established in 1974 by US Congress after the termination of the Tuskegee syphilis study. The Act authorized federal agencies to develop human research regulations, and in 1979 the Belmont Report was released, setting out principles of ethical research on humans in the USA.

In Ethiopia, no formal ethics approval process was in place between the 1960s and 1980s when Dr Price gathered the podoconiosis tissues and other materials currently in the archive. Internationally, the Declaration of Helsinki, adopted in 1964 at the 18th World Medical Association General Assembly, was the most influential set of guidelines in existence, but these were not legally binding and merely existed to facilitate and guide national legislation. Similarly, in the UK there were no formal ethics boards in place at the time, as NHS National Research Committees were not established until 1991 (Cave and Holm, 2002). Lack of ethical approval for collection or retention of samples was therefore consistent with standard practice at the time.

Secondly, we considered the time period that has elapsed since the establishment of the archive, and the impact of this on consent. In the case of this unique archive, three to four decades have passed, which brings to light concerns around whether consent was given for the samples to be collected or retained. The retrospective use of retained samples is sometimes permitted if donors are recontacted to consent to the specific research planned. The time interval since sample collection and the paucity of contact information would make it impossible to locate the donors in Ethiopia and gain further consent for contemporary research.

Archives inherit the curatorship of those data collected and are responsible for determining the ethical considerations, or lack thereof, of their day, in the context of its time and place. Owing to the time period that has elapsed since the archive was established, it is likely to be difficult to trace individuals linked to the archive, and also likely that many patients from whom samples were taken will have died. It therefore appears impracticable to reconsent or retrospectively seek approval for contemporary research.

In summary, although international guidelines on human research existed in the 1970s, very few countries had developed national legislation, regulations or ethics committees to oversee human research. Between the 1960s and 1980s, Dr Price was therefore acting as a reasonable health professional of his era in collecting and studying tissue samples from podoconiosis patients. Like many other health professionals at the time, he did not formally record consent even for his own immediate research, let alone for tissue storage and curation over long periods of time. However, he set an admirable example in publishing the results of his studies, which remain foundational to current research in podoconiosis.

What guidance currently exists on the use of a historical archive?

While exploring how the archived samples might be used and what types of permission or approval might be required, it became apparent that there was little guidance to support the appropriate use of the archive materials.

The Research Governance & Ethics Committee (RGEC) at BSMS was asked for guidance on use of an archive collected and moved to the UK before the UK Human Tissue Authority was set up following the Human Tissue Act legislation in 2004. The Committee recommended exploring the framework around the use of a historical archive such as this, and asked that the Human Tissue Authority be informed of its existence.

The Human Tissue Authority was contacted and confirmed that the archive did not meet HTA criteria given the period in which the tissues were collected. The HTA raised its own queries about the University of Sussex's HTA licensing status and whether the collection might be subject to public display. Both were addressed, and no further licensing action was required. The Human Tissue Authority's approach was relatively permissive in comparison to that relating to prospective sample collection, when guidance and legislation is more restrictive.

Wider exploration showed that there has been growing interest in the use of archived tissues in recent years, which has highlighted the need for clarification of guidance. Furthermore, there have been scenarios where the existing guidance has been interpreted by research ethics committees in very different ways. For example, a research group hoping to access an archive of human tissues for the

development of anticancer drugs were granted permission by one ethics council and rejected by another, based on the same guidelines by the Medical Research Council and the Royal College of Pathologists (Basu et al., 2003). The US National Bioethics Advisory Commission advises that any research that utilizes unidentifiable specimens already in existence and does not involve human participants is exempt from further ethics review or consent. The Royal College of Physicians takes a similar stance, stating, 'there is a continuing role for the non-consensual use of surplus tissue that is consensually removed as part of routine clinical care and which would otherwise be discarded, as long as participants are not inconvenienced in any way' (Royal College of Physicians, 2007).

The research team became aware of the European Society of Human Genetics (ESHG) policy, which states 'old collections should be regarded as abandoned and therefore usable for new research purposes as long as the institute's ethics committee approval is obtained'. The same guidance also discusses the importance of investigators obtaining informed consent from participants. However, in our case regarding the podoconiosis samples, given the anonymized nature of the tissue samples in the historical archive and the time that had elapsed since original collection, it was not feasible to reconsent or seek retrospective approvals for the use of the samples. In such scenarios, ESHG states that, 'an appropriate ethics review board should give its consent for further use of the samples based on the notion of minimum risk for the donor'. On the basis of this guidance, the research team submitted an application to their local RGEC to conduct new research on an abandoned collection.

It is clear that most of the guidance available focuses on the prospective approach, and very little literature exists on retrospective or old collections of tissues. Several authorities adopt a relatively unrestrictive approach and enable old samples to be used for contemporary research without reconsent. There is a great deal of variation in the interpretation of vague guidelines, and a lack of guidance around archived, existing, but unused or abandoned materials, leading to conflicting views from different ethics committees.

Is it unethical not to use the historical archive?

> It is a question of the future, the question of the future itself, the question of a response, of a promise and of a responsibility for tomorrow. The archive: if we want to know what that will have meant, we will only know in times to come. (Derrida and Prenowitz, 1998)

Several arguments for use of the archive were considered, including the broad principle of increasing access to research data through banking, and the unique nature of the archive.

Banking samples can add considerable value to research by opening them up for secondary uses. Open research frequently correlates with scientific rigour and improved recording, meaning it is more reproducible. It is also a more efficient use

of public money (Wicherts et al., 2011). Traditionally, researchers have been reluctant to share research resources and data, which often stems from concerns that errors may be uncovered if their work is reanalysed (Wicherts et al., 2011) or from concerns that researchers may not be able to comply with comparable ethical standards or research integrity expectations. However, as well as being a more efficient use of financial resources, open-access research often correlates with improved recording and better scientific research (Wicherts et al., 2011).

Banking in order to promote data sharing also increases the likelihood that any benefits of research conducted in low-income countries are disseminated equally among the citizens of the country in which the research, fieldwork or data collection takes place, as well as among the researchers and sponsors. The H3Africa project, jointly funded by the National Institutes of Health and the Wellcome Trust, is supporting the development of biorepositories to increase capacity for genetic research in Africa, and exemplifies the concept of equitable data dissemination (Tan, 2010). It is hoped that these biorepositories will encourage multidisciplinary collaborations between countries with the benefits being enjoyed by the citizens of those countries.

Although the Price archive is on a different scale from these large-scale biorepositories, the underlying principles are similar, with the prospect of wider use of the samples to understand podoconiosis aetiology and ultimately improve prevention and treatment in the endemic countries from which the samples originated.

Arguments against use of this archive of specimens for which consent was not collected to today's standards hinged on the loss of public trust in the UK following the organ retention scandal in Bristol, Alder Hey and Birmingham during the period of 1988 to 1995 which led to the Human Tissue Act of 2004. This loss of trust has been sustained by further international scandals, picked up by the wider media, relating to biomedical research involving the use of human biological material samples (Ashcroft, 2000). Public anxiety has been compounded by the perception of increased commercialization of research, and an increase in public discourse around patient rights and personal data, and examples where science has been considered more important than the privacy safety or well-being of research participants.

Some research demonstrates the public's willingness for tissue to be used in research. Furness and Nicholson (2004), when using a postal questionnaire to ask patients if surplus biopsy tissue could be used for research purposes, found that only 3.6 percent of respondents objected. This led the researchers to conclude that blocking or seriously delaying research is contrary to the public interest (Jones et al., 2003). In a similar vein, Ashcroft, when reflecting on the prospect of consent being sought retrospectively for reuse of archived tissues, stated that public trust can be established by open acknowledgement of the evolution of ethical standards and strict adherence to current best practice (Ashcroft, 2000). Both these perspectives suggest

that loss of trust is not irrevocable and that, given adequate explanation, patients and the public understand the importance of research on tissues.

If one is to argue that an archive should not be used, then issues around its disposal or further storage arise. Would the donors wish to have their tissues incinerated or otherwise disposed? The disposal of sensitive biological material from tissue samples relating to clinical tests is normal in Ethiopia; however, the cremation of deceased individuals is not practised by either the Orthodox Christian or Muslim communities; so, would donors allow tissues to be used for educational purposes? Should the tissues remain in storage, for how long, and what should be done if when the tissues become unusable? These and other difficult ethical considerations may arise if tissues are stockpiled without any defined purpose (Jones et al., 2003).

Conclusion

The RGEC agreed that it was inappropriate to apply current ethical standards to sample collection in the 1970s. The Committee decided to follow the European Society of Human Genetics view that old collections are usable for new research purposes, as long as there is minimal risk to the donor. The research team agreed there was minimal risk to the donor around current and future use given the lack of identifiable data linked to the samples.

In relation to consent, the RGEC and research team found support to proceed from the Medical Research Council and UK Department of Health,

> … to avoid making such collections unavailable for future medical research the Medical Research Council recommended that in the case of archival samples it may be appropriate for research to proceed without consent if it is impractical (or unethical) to trace patients and ask them for such consent. The UK Department of Health has followed broadly the same line. (Furness and Nicholson, 2004)

In consequence, the archive has been carefully catalogued and photographed. Tissue blocks have been prepared for both light microscopy and scanning electron microscopy to characterize the particles (i.e. identify the mineral phases) present in the samples. Further work using different sample preparation methods and microscopy techniques unavailable in Dr Price's day is on-going.

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